REMARKS

Claims 9-83 are now pending in the present application, of which Claims 9, 28, and 72-82 are presently withdrawn from consideration. Claims 1-8 were cancelled by previous amendment.

New Claim 83 recites a method for treating endogenous depression in a mammal by administering a therapeutically effective quantity of rotigotine or a metabolite, prodrug or physiologically acceptable salt thereof, to said mammal. Support for new Claim 83 is found in the specification as filed at least at paragraph **[0019]**.

No new matter is added, and no change in inventorship is believed to result from the present amendment.

RESPONSE TO OFFICE ACTION DATED 27 MAY 2010

1. Rejection Under 35 U.S.C. §103 over 6-Way Combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler and Dinan

Claims 10-20, 27, and 29-71 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 6 documents: U.S. Patent No. 4,501,890 (Nichols) in view of Pfeiffer (2002), Drugs Aging, 19(8): 561-570 (Pfeiffer), and in further view of U.S. Patent Publication No. 2005/0038015 (Bronzava), U.S. Patent No. 6,350,773 (Marquis), U.S. Patent No. 2003/0180332 (Rimpler), and U.S. Patent Publication No. 2005/0037983 (Dinan). This 6-way rejection is respectfully traversed.

The Office's sole rationale for establishing a *prima facie* presumption of obviousness is "there is an obvious to try and expectation of success for rotigotine to have anti-depressive activity because the compound of Nichols and rotigotine are both D_2 agonist[s] and treat Parkinson's disease. Thus, the method of treating depression and Parkinson's disease is effective through the D_2 agonist pathway." *See* Final Office Action, at p. 10. However, as set forth more fully below, Applicant presents evidence herein that rotigotine does not have D_2 agonist activity like the alleged compounds in Nichols. This is in addition to the vast structural difference which was discussed in Applicant's 10 Feb 2010 Response. Therefore, the Office's asserted rationale for an expectation of success is refuted.

1.1 Unlike the Nichols' Compounds, Rotigotine Is **NOT** Solely a D_2 Agonist.

Nichols states that the "compounds represented by Formulas III and IV are dopamine (D-2) agonists substantially devoid of other agonist or antagonist (blocking) activities." *See* col. 3, lines 20-23 (emphasis added). Contrary to the compounds reported in Nichols, rotigotine is not substantially devoid of other agonist or antagonist activity, and further rotigotine demonstrates a preference for the D_3 receptor not the D_2 receptor. Below is evidence of this fact.

"In standard binding assays, rotigotine demonstrated the highest affinity for dopamine receptors, particularly the dopamine **D_3** receptor (K_i = 0.71 nM) **with its affinities to other dopamine receptors** being (K_i in nM) $D_{4.2}$ (3.9), $D_{4.7}$ (5.9), D_2 (13.5), $D_{4.4}$ (15), and D_1 (83)...In newly developed reporter-gene assays for determination of functional activity, rotigotine behaved as a full agonist at dopamine receptors (rank order: $D_3>D_{2L}>D_1=D_5>D_{4.4}$) with potenticies 2,600 and 53 times higher than dopamine at dopamine D_3 and D_{2L} receptors, respectively...Thus, in respect to PD, rotigotine can be characterized as a specific **dopamine receptor agonist with a preference for the D_3 receptor over D_2 and D_1 receptors**." *See* Scheller, *et al.* (2009) Naunyn-Schmiedeberg's Arch Pharmacol 379:73-86, at 73 (emphasis added, and submitted herewith). Therefore, Nichols' compounds and rotigotine do not share the same D_2 agonist activity and thus the Office's rationale is in error and can not be used as a basis for establishing a reasonable expectation of success.

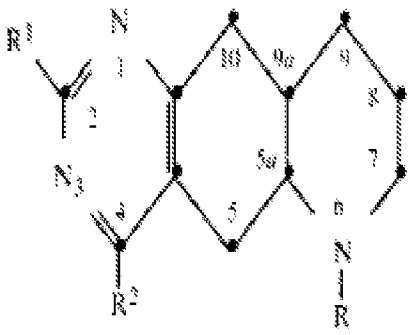
Furthermore, not only are the affinity profiles different, rotigotine's affinity profile actually de-motivates an ordinary artisan to select rotigotine for depression treatment. Wang, *et. al* (2007) Chinese J. of Physiology 502(2): 63-68 (herein "Wang" and submitted herewith) reports on the effects of apomorphine (APO), an agonist for the D_1 and D_2 receptors, and sulpiride (SUL), a selective D_2 antagonist, on the expression of learned helplessness behavior. Wang concludes that "the excessive stimulation of D_1 receptor may participate in the failure of coping behavior leading to learned helplessness and therefore in the pathophysiological mechanisms underlying the development of depression." As established above, rotigotine does have D_1 receptor activity. Therefore, the ordinary artisan would actually be de-

motivated to try rotigotine for depression in light of Wang's teaching against D_1 receptor stimulation.

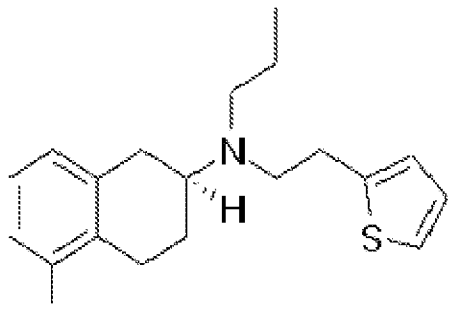
Lastly, an ordinary artisan appreciates that the fact a compound is a D_2 agonist, without any more evidence, does not establish that the compound will be able to treat depression. For example, Bertaina-Anglade in discussing effectiveness of dopamine agonists in the treatment of depression, reports clinical trials for the D_2-D_3 receptor agonist, pramipexole, yet still questions the efficacy of ropinerole, also a D_2-D_3 agonist. *See* Bertaina-Anglade, *et. al* (2006) European Journal of Pharmacology 548: 106-114 (submitted herewith). If one of ordinary skill in the art could predict efficacy from common affinity profiles, why would Bertaina-Anglade not be able to predict the effectiveness for ropinerole from pramipexole?

1.2 Rotigotine and the Nichols' Compounds Are Structurally Different

Furthermore, even if the receptor profiles were the same (which is not admitted herein), as set forth more fully in Applicant's 10 Feb 2010 Response, the compounds of Nichols are structurally different from rotigotine. Compare: Nichols' compounds represented by the following formula:



with rotigotine



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There is no evidence of record to suggest one of ordinary skill in the art could have predicted compounds, so chemically different, could both effectively treat depression.

1.3 Unreasonable Amount of Experimentation With No Guidance From Cited Art

As discussed above, the Examiner alleges that since Nichols teaches D_2 agonists for the treatment of depression, it would have been obvious to use rotigotine, a known D_2 agonist,

to treat depression. Not only do Nichols' compounds have different dopamine receptor activities and drastically different chemical structures compared to rotigotine, the amount of experimentation an ordinary artisan would have to perform to arrive at rotigotine for treating depression is unreasonable for at least the following reasons:

1. **Amount of Compounds to Choose From With No Guidance**: As explained in Applicant's 10 Feb 2010 response, the ordinary artisan would have had to first pick a compound considered to act on at least one dopamine receptor, then choose one that acted on at least the D_2 receptor but with a preference for D_3 (opposite of what is suggested in Nichols), and then select rotigotine (a dopamine receptor agonist with a preference for the D_3 receptor over D_2 and D_1 receptors). Accordingly, even if Nichols provides a pattern of preference for D_2 agonists devoid of other agonist or antagonist activities, there is no pattern of preference for choosing rotigotine with a completely different receptor profile. At best, the very large number of possible compounds (128 D_2 acting compounds, with at least 30 being D_2 agonists or partial agonists) provides an invitation to "try" or "experiment" on the large number of agonists.
2. **No Depression Examples in Nichols:** All of Nichols examples are synthetic preparation examples. There are no models of depression. Additionally, Nichols merely mentions a group of diseases such as hypertension, depression, anxiety, sexual dysfunction and Parkinson's disease. There isn't even a focus on depression in Nichols.

Moreover, not only is the amount of experimentation unreasonable, there is nothing within the cited documents, including Nichols, that provides any guidance to arrive at the claimed invention. It is apparent that in the instant case, "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." In re O'Farrell, 853 F. 2d 894, 903 (Fed. Cir. 1988). "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior

art possibilities, courts should not succumb to hindsight claims of obviousness." In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009), emphasis added.

In conclusion, there is no reasonable expectation of success at least because:

- Rotigotine does not share the same D_2 activity as the Nichols' compounds, and in fact demonstrates mixed dopamine receptor activity, favoring the D_3 receptor.
- The chemical structures of Nichols' compounds and rotigotine are vastly different.
- The amount of experimentation is too great to provide any predictability or reasonable expectation of success. In order for an invention to be "obvious to try", there has to be a finite number of identified, predictable potential solutions to the recognized need or problem. MPEP §2143, citing *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 385 (2007).

Therefore, for at least these reasons a presumption of pri*ma facie* obviousness has not been established.

1.4 Conclusion: 6-way 35 USC §103(a) Rejection

Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 11-20, 27 and 29-71 is nonobvious over Nichols in view of Pfeiffer, and in further view of Bronzava, Marquis, Rimpler, and Dinan for at least the same reasons that Claim 10 is nonobvious.

Withdrawal of the present 35 U.S.C. §103(a) rejection over the six-way combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler and Dinan is respectfully requested.

2. Rejection Under 35 U.S.C. §103 Over 8-Way Combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman

Claims 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 8 documents: Nichols in view of Pfeiffer, in further view of Bronzava, Marquis, Rimpler, and Dinan, and in further view of WO 02/089777 (Lauterbach) and U.S. Patent No. 4,769,028 (Hoffman). This 8-way rejection is respectfully traversed.

Claims 23-26 ultimately depend from Claim 10. Although not specifically rejected, a presumption of *prima facie* obviousness of Claim 10 (and thus of any claim dependent therefrom) over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman, or any combination of the 8 documents, does not exist. Hoffman and Lauterbach fail to cure the deficiencies of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof (see Section 1, above). Lauterbach reports on the measured effects of rotigotine only on Parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS). Depression is only one aspect of behavior and mood included in Part I of the UPDRS. However, Lauterbach does not teach that rotigotine has effective anti-depressive properties. Even if, *arguendo,* Hoffman "teach[es] a medical plaster that releases the active agent in a matrix and comprises adhesive properties" (Office Action, p. 7), Hoffman fails to disclose or teach rotigotine or depression. Accordingly, Hoffman does not provide any teaching or expectation regarding rotigotine's effect on the treatment of depression.

Since Lauterbach and Hoffman fail to cure the deficiencies of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof, the fact remains that rotigotine was not known to have antidepressant activity prior to the present invention. Therefore, the 8 cited documents, alone or in combination, fail to establish a presumption of *prima facie* obviousness of Claim 10.

Notwithstanding the Examiner's comments with regard to Claims 23-26, each of Claims 23-26 depend from Claim 10 and are nonobvious for the same reasons Claim 10 is nonobvious over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, Lauterbach and Hoffman or any combination thereof.

Withdrawal of the present 35 U.S.C. §103(a) rejection is respectfully requested.

3. Rejection Under 35 U.S.C. §103 Over 7-Way Combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas

Claims 21 and 22 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 7 documents: Nichols in view of Pfeiffer, in further in view of Bronzava, Marquis, Rimpler, and Dinan, and in further view of den Daas, et al. (1990) Naunyn-Schmeideberg's Arch Pharmacol, 342: 655-659 (den Daas). This 7-way rejection is respectfully traversed.

Claims 21 and 22 ultimately depend from Claim 10. Although not specifically rejected, a presumption of *prima facie* obviousness of Claim 10 (and thus of any claim dependent therefrom) over Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas, or any combination of the 7 documents, does not exist. Applicant incorporates its argument set forth in 10 February response, as (1) the results of the 7 esters tested in den Daas indicated that at least 4 of the esters did not have activity, and den Daas does not disclose, teach or suggest carbamate, carbonate, ketal, acetate, phosphate, phosphonate, sulfate or sulfonate prodrugs and (2) den Daas fails to cure the deficiencies of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, or any combination thereof, because the fact remains that rotigotine was not known to have antidepressant activity prior to the present invention. Therefore, the 7 cited documents, alone or in combination, fail to establish a presumption of *prima facie* obviousness of Claim 10.

Notwithstanding the Examiner's comments with regard to Claims 21 and 22, each of Claims 21 and 22 depend from Claim 10 and are therefore nonobvious for at least the same reasons Claim 10 is nonbobvious over the 7-way combination of Nichols, Pfeiffer, Bronzava, Marquis, Rimpler, Dinan, and den Daas.

Withdrawal of the present 35 U.S.C. §103(a) rejection is respectfully requested.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,
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